0022-202X/79/7305-0495$00.00/0
THE JOURNAL OF INVESTIGATIVE DERMATOLOGY, 73:495–500, 1979

Vol. 73, No. 5, Part II
Printed in U.S.A.

X. Pruritus, Pain, and Sweating Disorders

1. PRURITUS AND PAIN

Prevalence and Severity

Pruritus: Itching is by far the most common symptom of skin diseases and may also be associated with a variety of systemic disorders. When localized and transient, itching is a trivial nuisance but, when severe and generalized, it can become unbearable and totally disabling.

Eczematous diseases affect 3.5 million Americans, of whom 1.3 million have atopic dermatitis. In this disorder, a genetically determined, lowered itch threshold may well represent a major pathogenetic factor. It has been said of atopic dermatitis that "It is the itching that is eruptive, not the eruption that itches," implying that were itching prevented the disease could not occur or, if present, would rapidly clear.

A number of systemic disorders are sometimes associated with generalized itching. Two recent Scandinavian surveys have indicated that 1.5 to 3.0% of pregnant women develop significant itching. A 3% incidence of generalized itching in diabetics has been frequently cited; however, this estimate is based on a single study conducted more than 50 years ago. In polycythemia vera, severe generalized itching particularly after bathing, occurs in 10–30% of patients and may be the most disabling feature of the disease. Patients with lymphomas, especially Hodgkin's disease, frequently complain of intractable, generalized itching. It has been estimated that 30% may be so affected. Itching usually accompanies obstructive biliary disease and, in fact, may precede the development of jaundice by a year or longer. The number of patients with chronic renal failure undergoing hemodialysis is estimated at 30,000 throughout the United States. Of these, more than 50% complain of itching of variable severity, and in many the itching can be so severe as to be totally disabling. Generalized itching without primary cutaneous disease and without demonstrable systemic cause is not uncommon, particularly in the elderly.

Annual sales of topical antipruritic agents approximate $11 million, excluding about $100 million worth of topical corticosteroid preparations, sold annually, most of which are employed in the treatment of disorders in which itching is a prominent symptom.

Pain: Acute infections are the most common skin condition associated with pain. These present no particular problem since effective therapy is readily available. A more grave disorder is postherpetic neuralgia, a complication of herpes zoster which, when severe and prolonged, can be totally disabling. The annual incidence of herpes zoster has been estimated at about 2 per 1000: 400,000 cases in the United States each year. More than 60% of the patients are more than 45 years of age, and there appears to be an increased incidence between 60 and 70. Herpes zoster is even more common in patients with lymphoma or leukemia. In one study 9% of patients with Hodgkin's disease developed this complication.

The most frequent complication of herpes zoster is postherpetic neuralgia. This is uncommon in patients less than 50 years of age. Between the ages of 50–59, the incidence of this complication is 18%, from 60–69 it is 37%, over 70 it is almost 50%. The older the patient, the longer the duration of the pain. In almost half the patients over 70 pain lasts for more than one year and in many it may persist indefinitely. If a branch of the trigeminal nerve is involved, the likelihood of postherpetic neuralgia is still greater. According to a Mayo Clinic study, which may not be entirely representative, postherpetic neuralgia of more than one year's duration affects about 85,000 new patients annually. Since the disorder tends to last indefinitely, the actual number of sufferers must be many times this figure.

It is difficult to give a cost estimate of the more than 100,000 victims of postherpetic neuralgia. Most are totally disabled and the symptoms so distressing that suicidal attempts are not rare.

Prevention, Treatment, and Cure

Pruritis: When itching occurs as a symptom of systemic disease (chronic renal failure, lymphoma, cholestasis, hyperthyroidism), it usually fades or disappears entirely as treatment for the underlying condition becomes effective. Certain therapeutic maneuvers may hasten the desirable outcome. In chronic renal failure treatments consist of exposure of the skin to short-wave ultraviolet light, low protein diet, or treatment of associated secondary hyperparathyroidism. In cholestasis treatments consist of administration of cholestyramine, administration of immunosuppressants, and biliary drainage procedures.

Since itching is a symptom of a variety of cutaneous disorders, its control can best be accomplished by removal or alleviation of the underlying cause. In some instances prevention can be quite simple, as, for example, the use of chemicals to repel biting insects. In other cases, such as atopic dermatitis, the cause of the intractable itching is poorly understood and is probably due to many factors. Generalized pruritus in the absence of definable cutaneous or systemic causes presents an even more formidable problem because the underlying mechanisms are completely unknown.

In a small percentage of cases in which itching is histamine-mediated, as in urticaria, treatment with oral antihistamines is usually effective. In nonhistamine-mediated skin disorders, antihistamines are probably no more effective than sedatives and yet are widely used.

In most disorders associated with itching, treatment must be directed toward relief of inflammation. In these cases corticosteroids, both topical and systemic, are the mainstay of treatment. In no case, however, can they be considered curative. Cure results only in inherently self-limited disorders and these are clearly in the minority.

The lack of effectiveness of antipruritic therapy can be attested to by the enormous number of disparate therapies available. The physician has relatively little to offer. He can prescribe baths, wet dressings or lotions containing camphor, phenol, or menthol that substitute the sensation of cold for itching. An occasional patient will respond, for reasons unknown, to topical crotamiton, a scabicide, or to thiabendozle, an helminthicide, although the itch is due to reasons other than scabies or creeping eruption. Although topical anesthetics, such as benzocaine or dephenhydramine, can reduce the intensity of itching, these and related compounds produce allergic contact dermatitis in some users.

Many nonspecific, largely sedative measures have been recommended, such as bed rest, mild tranquilizers, and avoidance of rough clothing, overheating, alcohol, coffee, and hot foods. These are generally of little value. Those who consider itching a type of mild pain prescribe aspirin; the usefulness of aspirin is equivocal.

At present there is a paucity of research on itching and scratching. Discovery and characterization of the cutaneous receptor, understanding of the complex pattern of nerve impulses that are interpreted as itch, and greater knowledge of the biochemical events that take place within or around the nerve endings would spur the development of methods to control the symptoms.

Until recently, the usefulness of ultraviolet light for uremic itching was unsuspected. Perhaps this simple form of therapy will prove useful in other types of generalized itching. Wide gaps exist in our knowledge of the potential effectiveness of

acupuncture, transcutaneous nerve stimulation, and other electrophysiological and psychological approaches. Although unlikely to be curative, it is possible that further development of these incompletely explored methods could well lead to more effective means of control.

Pain: The patient with chronic postherpetic neuralgia is a therapeutic challenge. However, there is evidence that this complication may be preventable. Clinical studies indicate that oral corticosteroids given during the acute eruption significantly reduce the incidence of postherpetic neuralgia. Once the neuralgia is well-established, relief of pain is not easily achieved. Narcotics, although effective, carry a substantial risk of addiction since they must be used several times daily for prolonged periods. Several phenothiazine tranquilizers can provide considerable relief in some patients; significant untoward side effects often limit their use. In general, topical agents are of no value. Light freezing of the skin with Freon spray may occasionally be beneficial for weeks or months. The injection of long-acting corticosteroids into the skin has been claimed to be effective; no objective data are available to support the claim. Neurosurgical intervention may give relief but it is often followed by pain within a few months.

As with itch, the mechanism of cutaneous hyperalgesia has been incompletely defined. However, it is now known that damage to the skin leads to the local release or synthesis of pain-producing substances (PPS). Antidromic stimulation of pain nerve fibers leads to the release of pain-intensifying substances (PES). Chemical characterization of these substances and their biosynthesis could lead to the identification or development of specific inhibitors. Further clarification of the events occuring at the level of the first sensory relay nuclei would undoubtedly lead to improved electrophysiologic techniques for modifying the pain responses.

In herpes zoster, the causative virus lies dormant in the nerve ganglion until some precipitating factor(s) lets it propagate down the nerve fiber into the skin. In at least some cases the precipitating event is decreased immunity. This implies that an increase of immunity in highly susceptible persons (the elderly, Hodgkin's disease) may be effective in preventing this disorder and hence its complications.

The human skin is permeated by small nerves subserving the sensations of itch and pain. Since these nerves are not visible in routine histologic examination, their possible participation in disease processes has often been overlooked. Although methylene blue, silver stains, and cholinesterase reactions have been used to demonstrate abnormalities in the past, these techniques are too insensitive to detect subtle changes in nerve endings. Therefore, electron microscopy is the only morphological tool available for the examination of the nerve endings in the skin responsible for pain and itch.

Sensory nerves in the skin consist of two types: free nerve endings and those supplying organized receptors (Pacinian corpuscles, Meisner corpuscles, hair follicle end-organs and Pinkus' touch spots). Organized receptors are believed to be specific mechanoreceptors whereas free nerve endings are believed to subserve pain, itch, and other sensations.

The light microscopic term "free ending" indicates an absence of corpuscular structures surrounding the ending. Electron microscopic examination reveals however, that the axon is not "free." It is enclosed with a Schwann cell and basal-lamina throughout its course. The subepidermal horizontal network of nerve endings originates from nonmyelinated nerve fibers. Their point of origin is near the perikaryon of the terminal Schwann cell of the nerve sheath from which the endings emerge in a penicellate configuration. No specialized areas occur at the terminal of the axon; bulbous enlargements that might be such specialized areas are present infrequently along the length of the axon. The anatomic site of pain or itch reception is, as yet, unknown.

Intraepidermal nerve endings, frequently observed by light microscopists, have been assumed to be relevant to both pain and itching. However, with electron microscopy, intraepidermal nerves are rarely encountered suggesting their alleged function may be an incorrect assumption.

The primary reason for classifying itch as a separate sensory modality is that an itch feels different from any other sensation. It can be experienced in all gradations without other sensations intruding and provokes the desire to scratch. Itching can be produced by physical, chemical, mechanical, thermal, and electrical stimuli. Spots on the skin sensitive to itch can be demonstrated by mechanical pressure of a fine probe. Heat can produce itch if applied long enough at a nonpainful level. Monophasic square-wave electrical stimulation yields a reproducible itch response. In the induction of suction blisters, a mild-to-moderate itching occurs following the application of negative pressure. The sensation stops instantly if suction is interrupted and disappears abruptly when epidermal separation occurs. Itching may be the first sign of decompression sickness. This so-called "diver's itch" is thought to be due to the accumulation of microbubbles of nitrogen within the skin that either causes release of histamine or directly stimulates cutaneous nerves.

Numerous acids, alkalis and other nonspecific irritants can produce itching. Methyl bromide, for example, applied to normal skin sequentially produces itch, burning pain, and deep aching pain. The intradermal injection of histamine causes itching; intravenous injection does not. Spicules of cowage obtained from the pods of *Mucuna pruriens* produce severe itching when imbedded in the skin. These spicules contain an endopeptidase. Other peptidases, such as trypsin, chymotrypsin, and pepsin, are also potent pruritogens. Since all produce itching in the absence of a wheal and flare reaction and all are active in areas of skin depleted of histamine, the mechanism of itching produced by peptidases must be quite dissimilar to that induced by histamine. Dihydroxy bile salts applied to the skin under occlusion at acid pH produce itching; this itching is probably not due to histamine release. Because of the diverse nature of the known puritogenic stimuli it appears unlikely that a single mechanism subserves the itching response.

Attempts to identify the peripheral itch receptor or receptors have been numerous. Some investigators have concluded that itch is subserved by a C-fiber receptor population. However, data, derived from cat cutaneous nerve strands, do not exclude the possibility that the "itch sensation" arises from A-fiber activity. Histamine-induced itching remains constant until just before the skin becomes analgesic owing to asphyxia or cooling; this is consistent with the C-fiber theory. The delay in sensory response to itch produced by electrical stimulation also supports the C-fiber theory. On the other hand, two types of itch sensation have been reported as arising from different fibers: a "prickling itch," caused by myelinated fibers, and a "burning itch" caused by nonmyelinated fibers. Thus, there is no proof that itch is transmitted exclusively by C-fibers.

In the past, itch has sometimes been regarded as simply a type of weak pain. Considerable evidence negates this concept even though both itch and pain sensations are absent in patients with congenital indifference to pain. For example, itch and pain can both be experienced through a full range of intensities simultaneously in the same area and be separately recognized. Heating the skin abolishes itch and heightens pain. Removal of the epidermis and upper dermis eliminates the sensation of itch but not the perception of pain. At the central processing level pain and itch also differ in that itching elicits scratching whereas pain induces withdrawal. Furthermore, pain can be relieved by morphine alkaloids that may, in fact, intensify itching.

There is also the possibility that the sensation of itch may be subserved by a population of hitherto undescribed specific cutaneous receptors. Although cutaneous receptors have been carefully studied, receptors specific to pruritic stimuli have never been identified. They may have been overlooked because of technical difficulties, especially if extremely small fibers are involved, and because they may respond exclusively to pruritic substances and not to other adequate stimuli.

Although these data tend to provide clear separation of the

sensations of itch and pain, there is evidence that both can be suppressed by a variety of mechanical and thermal stimuli. Noteworthy are studies on the "antipruritic state." The common experience that scratching or pinching the skin transiently relieves itch led workers to study in great detail these competing stimuli. Pressure and vibration even of mild intensity in addition to pain suppressed itching. Light pinpricks, even at some distance from histamine-induced itching, provided relief if the painful stimulus was induced in the same dermatome. With more severe pain, such as pinching the skin with forceps, prolonged hyperalgesia occurred that prevented itch perception for a prolonged period. If, however, a local anesthetic was injected at the site of injury, itch could again be experienced.

Since all sensations are subjective, psychological factors may play a decisive role in their perception. Four major groups of psychological investigations have dealt with this problem. The ethologists, principally concerned with animal responses, have noted that animals scratch apparently in the absence of itching when in a situation that elicits two mutually exclusive behaviors. Typically, under such circumstances an animal does neither. Instead he stops to scratch. Similar behavioral patterns can, of course, be observed in man. Ethologists tend to ascribe scratching in animals, including man, to frustration and to blocking of drive states.

Psychoanalysts tend to relate scratching behavior to thwarted emotions arising from psychosexual complexities or to anxiety due to repressed, socially unacceptable drives. They also consider some forms of scratching as autoeroticism or cutaneous masturbation. In this respect they differ from the ethologists who have not observed this in lower animals.

Behaviorists have been primarily interested in the scratch-itch-scratch cycle. When scratching is performed in response to itch, the reduction of the itch sensation by scratching is reinforced, thus increasing the likelihood of additional scratching. At the same time, scratching increases tissue irritability so that itch is more likely to recur with increased intensity. Scratching behavior is thus reinforced, producing a habit pattern. Interestingly, a scratching response can be easily induced by Pavlovian conditioning so that a previous neutral stimulus can elicit scratching behavior in both man and animals.

Finally, trait theorists have attributed pruritic syndromes to constitutional, somatotypic predispositions, a hyperirritable autonomic nervous system, or to certain types of personality structure. Numerous studies in this field have resulted in little more than conflicting theories.

Status of Clinical Research

Pruritus: Bile salts are well-established as the cause of cholestatic itching. In this disorder the degree of itching is related to skin levels of bile salts and not to serum levels. Attempts to cause itching by systemic administration of bile salts have been unsuccessful. Topically, dihydroxy bile salts must be applied at acid pH under occlusion on stripped skin. Itching begins in about 18 hours, the delay reflecting the time required for diffusion or for the release of a secondary mediator.

Itching does not usually accompany renal failure of recent origin despite its severity. In chronic azotomia, itching is a frequent complaint and usually responds well to adequate dialysis and a low protein diet. However, some patients continue to itch despite apparent chemical control and many more itch during the dialysis period itself.

Although the mechanism of the pruritus is not well understood, some available data are pertinent. Subtotal parathyroidectomy has been reported effective in relieving pruritus in patients with chronic uremia and secondary hyperparathyroidism; this suggests that calcium and phosphorous play are particularly active in the genesis of the itching. However, parathyroidectomy has also been shown to be effective in the absence of hyperparathyroidism, and pruritus may be entirely absent in chronic uremia with chronic hyperparathyroidism. Thus, the role of calcium and phosphorous in pruritus is not clear. The success of ultraviolet light therapy in the relief of uremic pruritus is also unclear and paradoxical. Vitamin D, the level of which should be raised by this therapy, has been shown to reinduce pruritus in patients treated by subtotal parathyroidectomy. It is possible that histamine release also is causative since increased numbers of mast cells are found in the spleen, bone marrow, and skin of patients undergoing long-term hemodialysis.

There are few recent studies on pruritus in patients with skin disorders. One group has reported that night-scratching in atopic dermatitis tends to occur in introverted, neurotic individuals with substantial self-directed hostility and a strong tendency to avoid ambiguity, ambivalance, and conflict. Scratching might represent a conditioned response to itching. To study this, patients with lichen simplex and normal individuals were conditioned to scratch in response to a tone. The patients conditioned more readily and extinguished more slowly than the controls. Patients with histories of itching dermatoses showed a lower threshold for the perception of an electrically-induced itch stimulus. Clearly, these rudimentary clinical studies provide little insight into the nature of itching.

Pain: In postherpetic neuralgia, nerve fibers in the middle and lower dermis are destroyed; this can be demonstrated with silver impregnation techniques. Corresponding fibers in the spinal cord degenerate and scarring may occur in the sensory ganglia. The result is that sensory impairment is common in the affected area.

Needs for Additional Basic Research

Pruritis associated with inflamed or irritated skin: The goals of research in this area should be to identify substances in inflamed skin that excite itch receptors and to find ways of reducing the concentration of such substances or of blocking their action on nerve endings. Following are some specific research recommendations.

1. There are increased concentrations of histamine, prostaglandins, kallikrein, kinins, complement components, and cathepsins in itchy skin. Histamine causes itch when pricked into human skin. Other substances need to be studied as well in both normal subjects and those with inflammatory dermatoses, before and after pretreatment with antihistamines, 48/80, and morphine.

2. An enzyme in cowage spicules causes intense itching in human skin. Cowage principle should be characterized chemically and immunologically, as it may act similarly to pruritogens present in itchy skin. Itchy diseased skin could then be examined to determine whether any of these cowage-like products are present in high enough concentrations to account for the itch. Anticowage antibody could be developed in animals and used to measure cowage-like activity in itchy human skin. Substances found in high concentrations in itchy skin that cause itch when introduced into normal skin are reasonable suspects as pruritogens. After identifying pruritogens it should be possible to devise specific therapy to reduce their concentration or to block their action at the nerve endings.

3. Is itch always the result of high concentrations of pruritogens acting on normal nerve endings? Or in some cases might there be morphologic or physiological changes in the nerve endings? There should be studies to define the structure and low threshold points of itch receptors. For example, if the skin of normal and atopic animals were stimulated with cowage or other known pruritogens, recordings of nerve activity could be made from single sensory neurons. After identification of low threshold skin areas, the sites could be biopsied and studied microscopically to determine whether or not there are distinct morphological characteristics in itchy skin.

Pruritis in skin that appears to be normal: Itch may arise in uninflamed or apparently normal skin in many disease states. Its origin is unclear. Research should be conducted to determine whether itching in these diseases is the result of cutaneous receptor hyperactivity or central nervous system stimulation. In those diseases where it is clear that the itch arises at levels higher in the central nervous system than the skin receptors, a

search should be made for inhibitory transmitter substances that could reduce the activity of specific central neurons involved in itch.

Pain: The most pressing cutaneous pain problem is associated with postherpetic neuralgia. Why zoster patients are in pain is not known. It is important to provide continued support for research on the general neuromechanisms of pain. A search should be made for substances that inhibit those central neurons specifically involved in zoster pain.

At present, no animal model exists with which to study the underlying neural mechanisms in postherpetic neuralgia. Such a model should be sought.

Needs for Additional Clinical Research

Pruritis: Data from empirical approaches to itch therapy are not always collected in a systematic way, and rational judgments about the efficacy of such treatments are difficult to make. Research should be supported for carefully controlled studies on the use of ultraviolet light, acupuncture, and transcutaneous electrical stimulation as methods for controlling intractable itch.

Collaborative studies of dermatologists and psychologists should be initiated to determine whether itch can be controlled by reducing conflict and anxiety and by elevating the patient's sense of personal worth.

Pain: Carefully designed studies should be undertaken to document the effectiveness of currently available therapies for postzoster neuralgia. Patients in the early stages of the disease, as well as those with healed lesions but who remain in pain, should be used to study the effects of oral corticosteroids, adenine arabinoside, local cutaneous freezing of the affected dermatome, local ultraviolet radiation, intracutaneous electrical stimulation, acupuncture, and group psychotherapy.

2. SWEATING DISORDERS

Prevalence and Severity

Effects on quality of life: Generalized sweating is the normal response to exercise or thermal stress by which human beings control their body temperature through evaporative heat loss. Failure of this mechanism can cause hyperthermia and death. Interference with thermal sweating is a serious matter and may have serious consequences.

Sweating, particularly of the palms, soles, and axillae, in response to emotional stimulation is also normal and is generally only a cosmetic social nuisance. However, when severe and persistent, emotional sweating can be a handicap to employment and may predispose to other cutaneous diseases. Excessive sweating probably is a contributing factor to tinea pedis, which afflicts 7.5 million persons in the United States, to eczema of the hands, which afflicts 700,000, and to contact dermatitis of the feet, which afflicts countless others.

During the summer in temperate climates the sweat pores can be temporarily occluded producing miliaria. The disease particularly affects infants and is of minor import since it responds readily to simple cooling of the body. However, in the tropics, miliaria can become a serious problem. Add to this the impact of severe heat stress on individuals who are not acclimatized, to wit, military personnel stationed in the South Pacific in World War II. Under these conditions of extreme thermal stress, miliaria, tropical anhidrotic asthenia, heat exhaustion, and heat stroke can produce total disability in the majority of affected persons. In fact, these disorders probably are the leading cause of disability in United States soldiers in tropical theaters of operation.

Annual sales of antiperspirants in the United States approximate $500 million. These products are only marginally effective and have no applicability to the control of excessive sweating of the palms and soles. Add to this expenditures for treating diseases that sweating may aggravate. Approximately $100 million is expended annually for topical corticosteroid preparations, the major treatment for eczematous eruptions of the palms and soles, and additional millions are expended for topical and systemic antifungal agents used in the treatment of tinea pedis.

Present state: Eccrine sweat glands are largely innervated by unique postganglionic sympathetic fibers that release acetylcholine at the neuroglandular junction. However, safe dosages of anticholinergic drugs, either topical or systemic, are incapable of controlling excessive emotional sweating. Since thermal sweating constitutes the major means of heat loss in a hot environment, attempts to inhibit emotional sweating by systemic therapy can be dangerous. Tranquilizers are effective in some cases although their tendency to produce drowsiness limits their use. The topical application of formalin or gluteraldehyde solutions to the palms and soles can substantially inhibit sweating. However, formalin often causes allergic contact dermatitis and gluteraldehyde produces an objectionable discoloration. The alcoholic solutions of aluminum chloride that have recently come into use as antiperspirants seem to be more effective in controlling axillary sweating than sweating on the palms and soles.

Surgical removal of the major eccrine gland-bearing region of the axillae effectively controls sweating, a procedure not applicable to the palms or soles. Since the eccrine sweat glands receive their innervation from postganglionic sympathetic fibers, cervical or lumbar sympathectomy has been advocated in the control of extreme sweating of the palms and soles. However, this drastic operation often produces only temporary relief owing to the incompleteness of the procedure. Even when entirely successful it leaves the skin completely dry and patients appear more susceptible to eczema.

In the tropics asthenia and wide-spread miliaria can be prevented if a gradual acclimatization program can be instituted or if an air-conditioned environment is available for 8 hours daily. Neither of these is possible in the rapid deployment of military personnel from a temperate to a tropical climate.

Prospects for the future: Although our understanding of sweating mechanisms is far from clear, we know more about thermal sweating responses than emotional sweating responses. What is lacking is knowledge of events at the neuroglandular junction differentiating emotional and thermal response. Existing technology is sufficiently developed to deal with this problem. Given a concentration of resources and study in this area, effective control of emotional sweating could be achieved.

Status of Basic Research

Man has about 3 to 4 million eccrine sweat glands, each weighing 30 to 40 mg. These glands are distributed throughout the skin and have an aggregate weight of about one kidney. Together these glands can secrete a maximum rate of 2-3 liters/hr for several hours in an acclimatized individual.

Anatomically, the eccrine sweat gland consists of three major portions—a secretory coil, a duct and an intraepidermal sweat duct unit. The secretory coil produces a plasma-like precursor fluid. As this fluid passes through the distal portion of the duct, sodium is absorbed and the resulting hypotonic fluid passes through the proximal duct and the intraepidermal sweat duct unit onto the skin surface where it evaporates and cools the skin.

Functionally, eccrine glands appear to be of two types: those thermally responsive and those emotionally responsive. Eccrine glands on the general body surface respond primarily to thermal stress and regulate body temperature. Those on the palms and soles respond in addition, to emotional stimulation or direct pressure. These are analagous to the sweat glands on the friction surfaces of lower mammals. Embryologically, emotionally responsive sweat glands make their appearance during the third fetal month and thermally responsive glands during the fifth. Thermally responsive glands seem to be a uniquely human adaptive response. Unique among mammals, man with his relatively naked skin, relies on evaporation rather than insula-

tion or panting for protection against a hot environment. Among the primates man has evolved the most thermally responsive eccrine sweat gland system.

The secretory coil of the eccrine sweat gland of the human, the monkey, the cat, and the opossum consists of three distinct cell types: the secretory, clear (or large, pale) cell; the dark (or mucoid) cell; and the myoepithelial cell. Substantial evidence indicates that the clear cell produces the aqueous component of sweat and the dark cell the mucoprotein component. Interspersed among adjacent clear cells are intercellular canaliculi that open into the lumen of the secretory coil. Within the canaliculus the position of the "tight junction" in relation to the lumen confers upon this system the characteristics of a "backward transporting system." The myoepithelial cell functions mainly as a supportive structure for the delicate secretory apparatus although it is capable of contractions when stimulated by acetylcholine. This contraction is not essential for either sweat formation or expulsion since calcium ionophore will induce active sweating when the myoepithelial cell is absent.

The control center for thermal sweating resides in the hypothalamic area of the brain which, in effect, functions as a biologic thermostat. Efferent impulses descend through the brain stem and spinal tract, cross at various levels, and terminate in the lateral horn. Sympathetic postganglionic C fibers abundantly innervate the secretory coil, which pharmacologically reacts as if it were mainly parasympathetic or cholinergic. Histochemical techniques have recently identified a loose network of nerves containing catecholamine around the eccrine glands of the macaque. A similar dual innervation probably supplies the human eccrine glands as well, since they are responsive to both cholinergic and adrenergic stimulation.

Although data from innumerable studies on the function of the sweat gland *in vivo* are available, our present understanding is also based on results obtained from experiments on isolated glands *in vitro*. These studies indicate that sweating induced by acetylcholine is completely inhibited not only by parasympatholytic agents, such as atropine, but also by ouabain. This indicates that $Na^+ + K^+$ - activated ATPase plays a major role in sweat secretion. Ouabain also inhibits glucose utilization by the eccrine secreting coil, which suggests a linkage of energy production and sodium transport.

Samples obtained by micropuncture directly from the secretory lumen indicate that the sodium and potassium concentrations are approximately isotonic to plasma. Specimens from the proximal duct contain sodium concentrations less than 145 mM and potassium concentrations greater than 5 mM, indicating ductal reabsorption of Na^+ and possibly the secretion of K^+ into the sweat.

DibutyrylcyclicAMP, (DBcAMP) although ineffective in inducing sweating *in vivo* upon intracutaneous injection, produces, *in vitro*, a sweat rate about one-tenth that of acetylcholine. The addition of theophylline, a phosphodiesterase inhibitor, markedly increases the response to DBcAMP; the addition of epinepherine to BcAMP has no consistent effect. Theophylline, *per se,* can stimulate sweating, an effect not blocked by either atropine or phentolamine. Prostglandin E_1 also induces active sweating at a rate equal to that of cholinergic stimulation.

As in other glandular epithelia, calcium appears to be a critical element in sweat secretion. Sweating is totally inhibited in isolated glands *in vitro* by a calcium-free medium or by the removal of calcium from the medium by chelation with EDTA. Calcium ionophore, A23187, stimulates sweat secretion, an effect blocked by ouabain but not by atropine or propranolol. Thus, intracellular calcium stimulates the secretory process at a point beyond the site of action of cholinergic or adrenergic drugs. In fact, the primary function of acetylcholine may be the introduction of calcium into the cell. However, intracellular cAMP levels do not rise after A23187 is added to the medium, leaving unsolved the problem of how active transport is stimulated when only calcium is introduced into the cell.

To maintain its secreting function the sweat gland requires an energy supply. Glycogen within the secretory cells is apparently not a sufficient energy source since sweating in isolated glands does not occur in a glucose-free medium. Dependence on glucose does not decrease with acclimatization. The sweat glands in acclimatized persons contain little glycogen and yet are capable of producing a higher rate of sweating than glycogen-rich glands of unacclimatized persons. Degradation of glucose may occur in the secretory cells by four pathways: by incomplete oxidation to lactate via the Embden-Meyerhof glycolytic cycle; by the tricarboxylic acid cycle preceded by the production of pyruvate; by the oxidation reactions of the hexose monophosphate shunt; and by oxidation to the glucuronic acid. Some contend that anaerobic glycosis of glucose to lactate is the only energy source because studies were unable to detect consummation of oxygen by the isolated sweat gland. Other evidence is to the contrary: occlusion of the blood supply to an extremity markedly inhibits sweating and raises sweat lactate concentration; sweat glands isolated for study show high CO_2 production that can be arrested by cyanide, ouabain or atropine; 3, 4-dinitrophenol fully reverses the inhibition of glucose metabolism induced by ouabain.

The process of reabsorption of Na^+ from the distal sweat duct seems to involve active transport since $Na^+ + K^+$ - ATPase have been demonstrated in the duct and since ouabain inhibits NaCl absorption. Furthermore, the transepithelial potential difference is from 40 to 70 mV, lumen negative, in the duct, indicating that Na^+ must be transported against both an electrical and chemical concentration gradient. Incomplete data indicate that both H^+ - Na^+ and Na^+ - K^+ exchange mechanisms are involved in ductal reabsorption. Na^+ for K^+ exchange is facilitated by aldosterone and inhibited by aldactone. However, unlike the renal tubuli, antidiuretic hormone has no effect on ductal functions either *in vivo* or *in vitro*.

Status of Clinical Research

Most of the current research on eccrine sweat gland function is conducted by environmental physiologists concerned with the role of sweating in body temperature regulation during work and heat exposure. Although these studies are important in their own right, work is also needed to provide insight into the control of emotional sweating, which is a major factor in predisposing the skin, particularly the skin of the feet, to infections and eczema.

Dermatologists have attempted to control emotional sweating through the use of tranquilizers. They may afford relief, particularly in mild cases. Theoretically, the administration of anticholinergic drugs systemically should be effective, but in practice, these drugs tend to produce serious side effects even before appreciable decrease in sweating takes place. Available topical anticholinergic agents penetrate the skin of the palms and soles poorly and are, therefore, of no value. Although sporadic success has been reported for the use of iontophoresis, it enjoys little popularity. Tanning agents, such as formaldehyde and glutaraldehyde, definitely reduce palmar and plantar sweating, but the former is a contact sensitizer and the latter discolors the skin. Sympathectomy, when successful, simply substitutes an excessively dry skin for an excessively wet one; both are equally predisposed to disease.

Needs for Additional Basic Research

The sweat gland is accessible and physiologically manipulable *in vivo*. Sweat glands can be dissected alive from fresh skin biopsies for *in vitro* study. Basic studies should continue to be supported on the normal gland, both *in vivo* and *in vitro*. Such studies will provide not only further insight into secretory and reabsorptive processes within the gland but also new information about transport mechanisms and membrane function in general. The results from these studies may then be extrapolated to many other organs, such as the pancreas, salivary

glands, stomach, and intestine. Further definition of the physiology of the eccrine sweat duct may provide insight into the basic systemic defect in cystic fibrosis in which the decreased ductal reabsorption of sodium is a characteristic feature. It is not known why sweat glands are hyperactive in some persons. Studies should be pursued to determine if hyperactivity is the result of increased sensitivity at the sweat gland itself or at some more central level.

Needs for Additional Clinical Research

Hyperhidrosis is a problem on the palms, soles, and axillae of many persons. Despite the enormous investments by industry there is no safe and effective topical agent to reduce sweating. Attempts to find out whether the source of hyperhidrosis is central or peripheral should continue. Efforts to develop more effective systemic and topical agents for control of this significant problem should be made.

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